Increasing efficiency and quality by automation and consolidation of tests: the experience of a hospital-based laboratory

Sara Valverde, Luigi Penzo, Gianluca Gessoni
Service of Laboratory Medicine, Ospedale Civile Chioggia (VE)

ABSTRACT

In this study we evaluated efficiency and quality in our laboratory after the implementation of total laboratory automation for clinical chemistry and immunochemistry assays. Thermo EnGen pre-analytical automation with a track system connecting two Vitros Fusion 5.1 and two Tosoh AIA-2000 analyzers were implemented. For Vitros Fusion 5.1, CVs were <8% (within-run) and <10% (inter-assay), except for measurement of anti-streptolysin O titre (CV 22.7%-27.7%). For Tosoh AIA-2000 analyzers, within-run CVs were <10% and between-run CVs <11%. No drift effects were observed, neither there was any carry-over. When evaluating the functionality of the whole automation system, we observed a turnaround time (TAT) 90% <10 min for tubes needing check-in and exit only. For tubes needing check-in and centrifugation – exit cycle, TAT 90% was <30 min. Result availability for clinical chemistry and/or immunochemistry on-line analyzers showed a TAT 90% <120 min. The adopted automation system effectively reduced the labor associated with specimen processing, possibly decreasing the number of laboratory errors that occur with specimen sorting, labeling and aliquoting, and improved the integrity of specimen handling throughout steps of specimen processing.

INTRODUCTION

At the beginning of the 21st century, clinical laboratories are faced with many challenges, including reduced fee schedules, demand for faster turnaround times (TAT), diminished numbers of qualified technologists and request for larger test repertoires. To meet these challenges, laboratories are increasingly relying on automation (1-3). By moving from manual assays of single analytes to random access, multichannel, automated instruments, more tests can be performed, more frequently, and with fewer workers. Combining several of these instruments on a single platform for clinical chemistry and immunochemistry represents a further degree of consolidation (4, 5). However, there has been few examples of integration of traditional clinical chemistry and heterogeneous immunoassays (6-9).

In this paper, we report our experience in implementing full automation of traditional clinical chemistry and heterogeneous immunoassays by using a pre-analytical system connected with two couples of analyzers. Our aim was to evaluate functionality and practicability of the system, to determine whether improved efficiency would be achieved by integrating clinical chemistry tests with heterogeneous immunoassay testing and to test for possible effects on the quality of results (reproducibility, carry-over) as a result of consolidation.

MATERIALS AND METHODS

We evaluated a solution for complete automation of clinical chemistry and immunochemistry assays, implemented in our laboratory, which adopted a Thermo EnGen pre-analytical system composed of following modules: entry-exit, two centrifuges, decapper, aliquoter and a track system connecting four analyzers: two Vitros Fusion 5.1 (Ortho Clinical Diagnostics) and two AIA-2000 platforms (Tosoh Bioscience Italia). In this study, we considered 57 assays performed on serum and/or plasma samples. Analyzers were set with a symmetric configuration, so that two couples of identical analyzers were available.

The study consisted of two parts: an analytical performance evaluation and a functionality and practicability study. For the analytical performance evaluation, imprecision studies were performed using lyophilized control material [Bio-Rad Lyphochek assayed chemistry control level 1 (lot. 14001) and 2 (lot. 14002)

Corrispondenza a: Gianluca Gessoni, Service of Laboratory Medicine, Ospedale Civile, Via Madonna Marina 500, 30015 Chioggia (VE). Tel. 0415534400, Fax 0415534401, E-mail ggessoni@asl14chioggia.veneto.it

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for clinical chemistry, Bio-Rad Lyphocheck immunoassay plus control levels 1 (lot. 40221), 2 (lot. 40222) and 3 (lot. 40223) for immunochemistry]. Protocols for the analytical performance experiments were derived from CLSI guidelines (Table 1) (10-13). The functionality and practicability experiments were performed in a six-day time period and included ~4150 samples, producing ~14,500 test results. The evaluated items, using protocols based on CLSI documents, are reported in Table 2 (14, 15).

For statistical analysis, we used the MedCalc software version 11.1.

RESULTS

Imprecision results are reported in Tables 3 and 4.

Functional sensitivity, evaluated as reported in Table 1, was 5 μg/L for ferritin (FERR) and 1.1 mmol/L for glucose (GLUC).

The presence of drift was tested for 12 methods for Vitros Fusion 5.1 [aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatine kinase (CK), total cholesterol (CHOL), creatinine (CREA), GLUC, total proteins (TP), total calcium (CA), iron (FE), sodium (NA), potassium (K), chloride (CL)] and 6 methods for Tosoh AIA 2000 [FERR, thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), myoglobin (MIO), carcinoembryonic antigen (CEA)]. No drift effects were observed over a 8-h period for any of the tested methods.

Investigated methods for carry-over were GLUC, CK, lactate dehydrogenase (LDH) (Vitros Fusion 5.1) and FERR, α-fetoprotein (AFP), β-human chorionic gonadotropin (Tosoh AIA 2000). No significant sample related carry-over effect was observed.

We decided to assume an interference >10% as significant. None of the considered methods showed a bias >10% up to a concentration of 500 mg/dL of triglyceride; TP and CREA showed a bias >10% in presence of high concentrations of bilirubin (200 μmol/L). As expected, concentrations of some analytes (AST, CK, FE and K) showed a significant bias in presence of hemolysis, even at low concentrations of hemoglobin (50 mmol/L).

Table 1
Evaluation protocols for the analytical performance evaluation study

Imprecision	*Within run:* Performed on one day, one run with 21 aliquots, using control materials with different concentrations of the analyte. Evaluation performed for each analyte. *Between run:* Control materials with different concentrations of the analyte were used over 21 days. Imprecision is derived from the second result of triplicate measurements. Evaluation performed for each analyte.
Functional sensitivity	Three serum pools were diluted to five different concentration levels of glucose and ferritin. They were aliquoted and stored at −80° C. Aliquots were determined over ten days in triplicates. Functional sensitivity was defined as the concentration at which inter-assay CV is 20%.
Drift	A control serum was measured every 30 min during 8 h for selected analytes to confirm the reagent stability. At time zero the baseline value was determined as the median value of triplicate measurements. The percent recovery from the baseline value was taken as measure for drift effect.
Carry-over	Measurements of three aliquots of a high-concentration sample (H1-H3) were followed by measurements of three aliquots of a low-concentration sample (L1-L3). This series was repeated 10 times. If a carry-over effect exists, L1 is the most influenced, L3 the least influenced aliquot. The sample-related carry over median (L2) was compared with the imprecision of the low-concentration sample.
Interferences	A serum with concentrations at the relevant decision level was spiked with the interfering substance and a dilution series of ten dilution steps was prepared with the same baseline serum. The different analytes were measured in triplicates. The concentration of the interfering substance was related to the serum index of the instrument. The percent recovery of the baseline value from the corresponding analyte was calculated for each dilution step. The methods tested were aspartate aminotransferase, creatine kinase, creatinine, iron, glucose, sodium, potassium and chloride for hyperbilirubinemia, hyperlipemia and hemolysis.

Table 2
Evaluated items in functionality and practicability studies

Turnaround time (TAT)	TAT for tubes (both for on-line and off-line analyzers) TAT for tests (only for on-line analyzers)
Test distribution	For on-line analyzers, test and tube distribution was recorded between the two couples of analyzers
Problem handling	Capability of problem handling of the integrated system (EnGen, Fusion 5.1, AIA) was evaluated for the following issues: sample integrity, reagent management, reflex tests, reruns for abnormal results

The functionality of the EnGen pre-analytical system was evaluated for TAT defined for tubes as the time between check-in and exit and for tests as the time between check-in and result availability. Table 5 reports TAT observed for tubes and tests in the same period. Moreover, the ability to handle and solve problems related to the integrated system was evaluated to check capability of managing common problems, such as control of samples, reagent management, reruns for abnormal results and the aliquoting function. Non-conformities were manually recorded (Table 6).

The resource analysis showed that after the completion of training period, full operability of the new automation required five full-time technicians; before implementation of the automation, six full-time technicians were required to perform the same operations on discrete analyzers. Moreover, productivity increased from 83,000 tests/year for technician in 2005 to 150,000 in 2012.

Table 3
Imprecision results for Vitros Fusion 5.1 analyzers

	Within-run CV, %		Between-run CV, %	
	Level I	Level II	Level I	Level II
Chloride	1.6	1.4	1.6	2.2
Potassium	2.0	1.8	1.8	1.4
Sodium	0.6	1.8	2.1	1.6
Inorganic phosphorus	1.4	1.2	1.5	1.2
Magnesium	3.0	2.6	3.4	3.7
Calcium	1.5	1.8	2.1	1.6
Iron	5.9	5.2	6.2	5.8
Alanine aminotransferase	4.6	4.0	7.2	5.6
Aspartate aminotransferase	2.7	2.4	3.4	2.7
Alkaline phosphatase	3.8	3.3	3.2	2.5
Amylase	6.3	5.5	7.1	5.5
Creatine kinase	3.6	3.2	3.9	3.0
Lactate dehydrogenase	4.5	4.0	8.1	6.3
Cholinesterase	2.2	1.9	2.6	2.0
Lipase	1.9	1.7	2.2	1.7
γ-Glutamyltransferase	1.1	1.0	2.2	1.9
Glucose	2.4	2.1	2.5	2.0
Total proteins	2.2	1.9	2.4	1.9
Urate	3.4	3.0	4.1	3.2
Tryglyceride	1.9	1.7	1.9	1.5
Total cholesterol	2.0	1.8	2.1	1.6
Creatinine	2.2	1.9	2.5	2.0
Urea	1.9	1.7	2.1	1.6
Total bilirubin	2.5	2.2	2.8	2.2
Digoxine	6.2	5.5	9.9	7.7
Theophylline	2.2	1.9	3.4	2.7
Phenobarbital	4.3	3.8	6.2	4.8
Phenytoin	2.4	2.1	2.5	2.0
Carbamazepine	8.0	7.0	9	7.0
C-reactive protein	5.1	4.5	6.7	5.2
Rheumatoid factor	4.5	4.0	6.6	5.1
Anti-streptolysin O titre	3.7	3.3	22.7	27.7

Table 4
Imprecision results for Tosoh AIA analyzers

	Within-run CV, %			Between-run CV, %		
	Level I	Level II	Level III	Level I	Level II	Level III
Carcinoembryonic antigen	3.3	2.4	2.9	3.3	2.6	3.6
α-fetoprotein	3.4	2.4	3.0	3.5	2.7	3.9
CA 15-3	3.9	2.8	3.4	6.4	5.0	7.0
CA 19-9	3.9	2.8	3.4	4.5	3.5	5.0
CA 125	2.5	1.8	2.2	5.0	3.9	5.5
Prostate-specific antigen	4.1	3.0	3.6	4.5	3.5	5.0
β-Human chorionic gonadotropin	3.9	2.8	3.4	4.6	3.6	5.1
Cortisol	4.5	3.2	3.9	4.7	3.7	5.2
Prolactin	7.1	5.1	6.2	7.5	5.9	8.3
Progesterone	5.5	4.0	4.8	5.8	4.5	6.4
Testosterone	7.8	5.6	6.8	8.0	6.2	8.8
C-peptide	6.9	5.0	6.0	7.1	5.5	7.8
Thyroid-stimulating hormone	6.9	5.0	6.0	6.9	5.4	7.6
Estriol	6.4	4.6	5.6	6.7	5.2	7.4
Follicle-stimulating hormone	6.5	4.7	5.7	7.0	5.5	7.7
Free triiodothyronine	4.7	3.5	4.2	4.9	3.8	5.4
Free tetraiodothyronine	4.8	6.2	7.5	10	7.8	11.0
Insulin	6.8	4.9	5.9	7.1	5.5	7.8
Luteinizing hormone	5.2	3.7	4.5	5.5	4.3	6.1
Ferritin	2.9	2.1	2.5	3.6	2.8	4.0
Folate	1.5	1.1	1.3	1.7	1.3	1.9
Vitamin B_{12}	9.8	7.1	8.5	9.9	8.7	10.9
Troponin I	9.5	6.8	8.3	9.9	7.7	10.9
Myoglobin	2.3	1.7	2.0	3.4	2.7	3.7
Creatine kinase MB	4.8	3.5	4.2	5.2	4.1	5.7

Table 5
Mean turnaround time (TAT) 90% (min) for tubes and tests on the evaluated system

Day	Tubes				Tests	
	No.	A	B	C	No.	D
Monday	884	10	25	100	2963	105
Tuesday	772	10	30	90	2855	95
Wednesday	633	10	30	95	2685	90
Thursday	758	10	30	95	2616	95
Friday	767	5	30	115	2473	120
Saturday	336	5	25	50	951	45

TAT for tubes was calculated from check-in to check-out in the EnGen automation. A, tubes for off-line analyzers, only check-in and sorting; B, tubes for off-line analyzers, check-in, sorting, centrifugation, decapping and aliquoting; C, tubes for on-line analyzers; D, only tests performed in on-line analyzers.

Table 6
Results for test distribution and problem handling

Tests distribution	Vitros Fusion 5.1 analyzer A, 58%; analyzer B, 42% Tosoh AIA 2000 analyzer A, 49%; analyzer B, 51%
Aliquoting	Performed 215 aliquots, failure in 3 (1.4%) due to label problems
Reagent managements	No problems were observed
Sample managements	49 (1.1%) tubes with failure of bar-code reading, mainly due to label incorrect positioning
Rerun for abnormal results	Performed 531 rerun, no problems observed
Dilution for abnormal results	Performed 127 diluitions; in 3 (2.3%) need of further manual dilution for results exceeding linearity after automatic dilution

DISCUSSION

The changing landscape of clinical laboratory has experienced the introduction of area of automation to meet challenges of technological advancements. Advanced and improved instrumentations, equipments and dedicated softwares are constantly being developed and become available for use. However, the individual needs may vary from one laboratory to another. Therefore, the automation should be sufficiently flexible to encompass different applications and should nevertheless be able to fill specific niches depending on individual requirements. Total laboratory automation may be seen as the combination of computerized sample tracking with automated sample handling, preparation and analysis, resulting in a full analytic process with minimal human involvement. These integrated systems increase productivity and improve data integrity, linking the data generation with analyzers and data storage. Total laboratory automation should be well planned. Considerations should be made concerning available space and laboratory layout. Adequate training and experience of people working with the technology should also be ensured and time must be allocated to allow for this process. In addition, responsibilities for system installation, programming, maintenance and final routine operation have to be addressed (16-18).

This study considered both the performance of analyzers and automation characteristics. The overall assessment can be rated as positive. For the first time in our laboratory, there was the opportunity to combine various laboratory segments with an extensive repertoire for general chemistry, specific proteins, drugs and immunochemistry tests on a multiple integrated analytical platform.

Analytic performance for Vitros Fusion 5.1 and Tosoh AIA-2000 had been partially previously evaluated (19-21). This study included an extensive analytic performance evaluation; intra- and inter-assay imprecisions were tested for the most important tests. When testing Vitros Fusion 5.1 analyzers, typical within-run CVs were between 2% and 5% and inter-assay CVs were between 1.5% and 6.0% for electrolytes, enzymes and substrates. We can emphasize that heterogeneous fluorescent immunoassays, evaluated on Tosoh AIA-2000 analyzers, showed reproducibility similar to that of chemistry tests, with intra-assay CVs between 2.5% and 7% and inter-assay CVs between 3% and 8%. Desirable quality specifications for imprecision were obtained from literature (22, 23). For control materials with concentrations in the physiologic range we observed CV values exceeding established goals for CL, NA and CA (Fusion 5.1) and for prolactin, testosterone and C-peptide (AIA 2000).

Functional sensitivity should be considered as an additional quality indicator for imprecision (24). In this study we determined the functional sensitivity of FERR using Tosoh AIA-2000 analyzers and GLUC using Vitros Fusion 5.1 analyzers. Reliable measurements at both high and low plasma FERR concentrations are important for clinical decision making. FERR was measurable down to the manufacturer-specified limit of 5 μg/L. This means that this FERR assay can be used confidently to diagnose iron deficiency. Reliable GLUC quantification even at very low concentrations is of great importance in the diagnosis and management of hypoglycemia. GLUC was measurable down to the manufacturer-specified limit of 1.1 mmol/L.

In the carry-over study, no sample-related carry-over was observed. Both Vitros Fusion 5.1 and Tosoh AIA-2000 adopt similar approaches in sample and reagent management to avoid carry-over due to samples or reagents. To minimize sample-related carry-over, both adopt disposable tips for sample aspiration and dispensation. The Vitros 5.1 analyzer uses two different main analytic technologies: MicroSlide and MicroTip. MicroSlide dry-chemistry technology is adopted for common clinical chemistry tests. MicroTip technology is adopted for drugs testing, specific proteins and user-defined applications. The liquid-phase reaction occurs in sealed plastic disposable micro-tips, in which the antigen-antibody reaction is detected by turbidimetric reading. Neither of these technologies require drains, plumbing, fixed probes or mixing assemblies, and the risk of contamination is virtually absent (20, 21). The Tosoh AIA-2000 adopts all-in-one test-specific bar-coded disposable reagents cups. The reaction takes place in these cups, from sample dispensation to antigen-antibody reaction, washing and separation of unbound components and addition of further reagents; the detection uses bichromatic fluorescence kinetic measurement. As there is no transfer of reagents the risk of contamination is drastically minimized (19).

The workflow strongly depends on the laboratory environment, the sample loading pattern and on the system configuration. In our opinion, the solution adopted in our laboratory offers the necessary flexibility. Processing times for sample groups requiring only

clinical chemistry tests and those requiring a mix of clinical chemistry and immunochemistry tests were similar, thus showing that there was no relevant increase when combining photometry, ion-selective electrode measurements and immunochemistry. In our setting, the Thermo EnGen system assured pre-analytical automation for all tubes coming into laboratory: tubes for off-line analyzer requiring check-in only, i.e. tubes for hematology analyzers, tubes for off-line analyzers requiring check-in and centrifugation, i.e. tubes for coagulation tests, tubes for on-line analyzers, i.e. clinical chemistry, drug monitoring, hormones, tumor and cardiac markers. As part of the functional study, we evaluated TAT 90% for tubes and assays. This parameter was defined as the time to process 90% of the total number of tubes (or assays) from check-in to two end-points differentiated for tubes (check-out) and assays (result availability), separately for routine and STAT samples. These registrations were performed for six consecutive days from Monday to Saturday. We observed in some days (Wednesday, Saturday) a slightly higher TAT 90% for tubes than for tests. This observation could be explained by considering two aspects: TAT for tubes included both tubes for on-line and off-line analyzers, and tubes for on-line analyzers were stored in a buffer area and were send to the entry-exit module only after the release of results. In this study we are unable to perform an evaluation of TAT in STAT samples, because in our hospital STAT samples reach the laboratory in a different manner, using dedicated containers. These samples are manually selected, off-line centrifuged and inserted into dedicate positions in the Thermo EnGen pre-analytic system.

In our laboratory a total of 5.0 full-time equivalent (FTE) technicians are allocated to operate the automation during the day shift for maintenance, calibration, quality control, sample and reagent loading, validation of analytic runs, test production and delivering of results to the laboratory information system. These five technicians perform over 750,000 tests/year, while in 2005, before the implementation of automation, the productivity in our core lab was about 83,000 tests/year each FTE. It should be noted that, before the implementation of automation, additional FTE were required to perform sample check-in and tube sorting, hematology and coagulation testing and transport of samples to the special chemistry area.

CONCLUSIONS

When evaluating new analytical solutions, it is important to determine whether the new systems can achieve their potential in real life, where a number of variables come into play. The number of interactions increases substantially as the number of different test methods run on an analyzer increases. The main advantages of the system tested here were efficiency, gained through workstation consolidation and automatic rerun, ease of use and training, high throughput combined with high reliability of results and versatility offered by an extensive test menu and ability to expand the system. Discussions on laboratory automation focus today on workstation consolidation, by combining a number of traditionally distinct methodologies on a single analyzer. The project realized in our laboratory offers this kind of workstation consolidation, with over 100 methods available, encompassing electrolytes, chemistry testing, specific proteins, drugs, toxicology, hormones, tumor markers and other immunoassays. Furthermore, this realization provides additional flexibility and capabilities, allowing, for example, the processing of STAT samples for the full testing repertoire while processing the regular workload. Additionally, if it turns out that one has initially underestimated the test repertoire or the required throughput, there is the flexibility for adding further modules to the system. A relevant criterion for evaluating system's effectiveness is TAT. We observed that usually within less than 105 min more than 90% of results were completed. Our preliminary results need, however, to be confirmed under effective routine conditions, where instrumental failures, pathological samples needing reruns, reagent change-over and calibrations could increase TAT significantly.

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